IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Kazuhisa HATAKEYAMA	:	Docket No. 2000-0644A
Serial No. 09/576,715	:	Group Art Unit 1655
Filed May 23, 2000	:	Examiner B. Forman
METHOD FOR GENE ANALYSIS	:	THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEES FOR THIS PAPER TO DEPOSIT ACCOUNT NO. 23-0975

AMENDMENT AFTER FINAL

Assistant Commissioner for Patents,
Washington, D.C. 20231

RESPONSE UNDER 37. CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1655

Sir:

Responsive to the Official Action dated August 6, 2001, the time for filing thereto being extended for one month in accordance with the Petition for Extension submitted concurrently herewith, please amend the above-identified application as follows.

In the Claims:

Kindly cancel claim 9 without prejudice.

1. (Twice Amended) A method of gene analysis by detecting hybridization between a probe nucleic acid and a sample nucleic acid comprising a target sequence complimentary to that of the probe nucleic acid, wherein at least one of the probe nucleic acid and the sample nucleic acid is DNA, said method comprising:

providing a substrate on which either the probe nucleic acid or the sample nucleic acid is immobilized,

adding the other non-immobilized probe nucleic acid or non-immobilized sample nucleic acid on the substrate, said other non-immobilized probe nucleic acid or non-immobilized sample nucleic acid being labeled with a flourescent substance,

performing hybridization of the probe nucleic acid and the sample nucleic acid in the presence of a double-stranded DNA-binding protein having a function to stabilize a complementary double-stranded DNA,

detecting the hybridization of the probe nucleic acid and the sample nucleic acid from the presence of said flourescent substance, and

performing gene analysis based on the hybridization detected.

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10. (Twice Amended) The method according to claim 1, wherein the amount of the sample nucleic acid comprising the target sequence is analyzed based on the intensity of a hybridization signal obtained from the hybridization of the sample nucleic acid and the probe nucleic acid, said hybridization signal being represented by the presence of said flourescent substance after hybridization.

11. (Twice Amended) The method according to claim 1, wherein the detection of the hybridization is performed by using a plurality of probe nucleic acids and detecting the polymorphism in the target sequence by comparing the intensity of each hybridization signal obtained from the hybridization of the sample nucleic acid and the plurality of probe nucleic

acids, said each hybridization signal being represented by the presence of said flourescent substance after hybridization.

12. (Twice Amended) The method according to claim 1, wherein the detection of the hybridization is performed by using a plurality of probe nucleic acids and detecting nucleotide sequence of the sample nucleic acid by comparing the intensity of each hybridization signal obtained from the hybridization of the sample nucleic acid and the plurality of probe nucleic acids, said each hybridization signal being represented by the presence of said flourescent substance after hybridization.

13. (Twice Amended) A test kit for detecting hybridization between a probe nucleic acid and a sample nucleic acid comprising a target sequence complementary to that of the probe nucleic acid according to the method of claim 1, which test kit comprises at least a double-stranded DNA-binding protein having a function to stabilize a complementary double-stranded DNA.

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Claim 9 has been cancelled without prejudice, and claims 1 and 10-13 have been amended to more particularly define the claimed features of the present invention. Support for

the claim amendments is readily apparent from the teachings of the specification and the original claims. Specific support for the phrase "labeled with a flourescent substance" can be found on page 12, lines 23-26, page 18, lines 9-16, and page 31 of the specification.

With regard to the rejection of claims 1-12 under 35 USC § 112, second paragraph, this rejection is believed to be overcome by the amendments to the claims. Specifically, claim 1 has been amended to recite a positive active method step for gene analysis as per the Examiner's request. Further, the hybridization step in claim 1 has been amended to clarify that hybridization is being performed between the probe nucleic acid and the sample nucleic acid in the presence of a double-stranded DNA-binding protein having a function to stabilize a complementary double-stranded DNA. Applicants believe that the amendments to claim 1 sufficiently address the Examiner's concerns and that this rejection under 35 USC § 112, second paragraph, can no longer be sustained and should be withdrawn.

With regard to the rejection of claims 1-12 under 35 USC § 103(a) as being unpatentable over Guagliardi et al. (M. Mol. Bio. 1997, 267: 841-848) in view of Dramanac (USP 6,025,136, filed August 28, 1997) and SwisProt (accession No. 059631, December 15, 1998 and accession No. P39476; P81550, February 1, 1995), this rejection has been deemed to be untenable and is thus respectfully traversed.

To establish a *prima facie* case of obviousness, the cited references in combination must teach or suggest the invention as a whole and include all the limitations of the claims. Here, in this case, none of the cited references, in the combination set forth by the Examiner, teaches or suggests all the limitations of the claims.

The object of the present invention is to provide a method for gene analysis quickly and efficiently with high precision and high sensitivity by performing hybridization in the presence of a double-stranded DNA-binding protein having a function to stabilize a complementary double-stranded DNA. The present invention uses a fluorescent substance as the labeling compound which is generally regarded as having a lower sensitivity and lower S/N ratio than a radioactive labelling compound. Furthermore, the present invention can perform gene analysis in a high-throughput manner even when using long chain nucleic acids. This is because the method of the present invention can be performed under high temperature, for example, at 60°C and at high speed.

In contrast, the cited reference, Guagliardi et al., discloses a method of gene analysis by using the protein Sso7d and performing a band shift assay with electrophoresis using radioactive compound as the labeling compound. This method cannot perform gene analysis in a high-throughput manner since the gene analysis cannot be performed at high speed using a plurality of samples, due to the low detection sensitivity of hybridization in this method and the long time required for assay.

Dramanac et al. disclose a method of gene analysis by immobilizing a nucleic acid on a substrate. However, the method of Dramanac et al. requires a long time for reaction under low temperature and a washing step even when using short chain nucleic acids. Furthermore, the method of Dramanac et al. is performed by using a radioactive compound as a labeled probe because of low sensitivity.

Thus, Guagliardi et al. and Dramanac et al. teach a method of gene analysis with low sensitivity even when using radioactive substance as the labeling compound and do not disclose a method of gene analysis having high precision, sensitivity and speed using fluorescent substance as the labeling compound. Therefore, since the combination of Guagliardi et al., Dramanac et al. and SwisProt fails to teach or suggest all the limitations of the claims (for example, fluorescent substance as the labeling compound), this rejection cannot be sustained and should be withdrawn.

The Examiner has also indicated that the Rule 1.132 Declaration filed June 12, 2001 is insufficient to overcome the rejections of claims 1-13 because the showing is not commensurate in scope with the claims as set forth in the last Official Action. The Examiner believes that the Declaration only refers to the system described in the above-referenced application and not to the individual claims of the application. Specifically, the Examiner notes that the claims are drawn to a method of gene analysis comprising immobilizing either the probe or sample nucleic acid; hybridizing probe to sample nucleic acid; performing hybridization; and detecting the hybridization. The Examiner believes that while the Declaration illustrates comparing hybridization signals between perfect match and mismatch hybrids in the presence or absence of Sso7d, the Declaration does not illustrate the claimed method of gene analysis.

However, Applicants respectfully and strongly disagree with the Examiner's reasoning in this regard. The most important step in a method for gene analysis is performing hybridization and detecting the hybridization. In other words, if hybridization can be detected with high sensitivity, gene analysis can be performed quickly and efficiently with high precision and

excellent results. In the Declaration filed June 12, 2001, the presently claimed combination of immobilizing either a probe nucleic acid or a sample nucleic acid on a substrate, using a double-stranded DNA-binding protein having a function to stabilize a complementary double-stranded DNA and using a fluorescent substance as the labeling compound, ***makes the hybridization signal intensity stronger and background lower***. Therefore, the present invention allows gene analysis to be performed with high speed and high sensitivity using a plurality of samples.

In contrast, none of the references cited by the Examiner disclose or teach the features and effects of the present invention noted above.

Thus, for the reasons recited above, the present invention is unobvious over the combined teachings and suggestions of Guagliardi et al., Dramanac et al. and SwisProt.

With regard to the rejection of claim 13 under 35 USC § 103(a) as being unpatentable over Guagliardi et al. (M. Mol. Bio. 1997, 267: 841-848) in view of Stratagene (catalog 1988, page 39), this rejection is also deemed to be untenable in view of the wording of amended claim 13 and is thus respectfully traversed. Specifically, claim 13 has been amended to depend on claim 1 which, for the reasons noted above, is allowable. Thus, claim 13 is also allowable for the reason noted above.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

In view of the foregoing amendments and remarks, it is respectfully submitted that the Application is now in condition for allowance. Such action is thus respectfully solicited.

If, however, the Examiner has any suggestions for expediting allowance of the application or believes that direct communication with Applicants' attorney will advance the prosecution of this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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